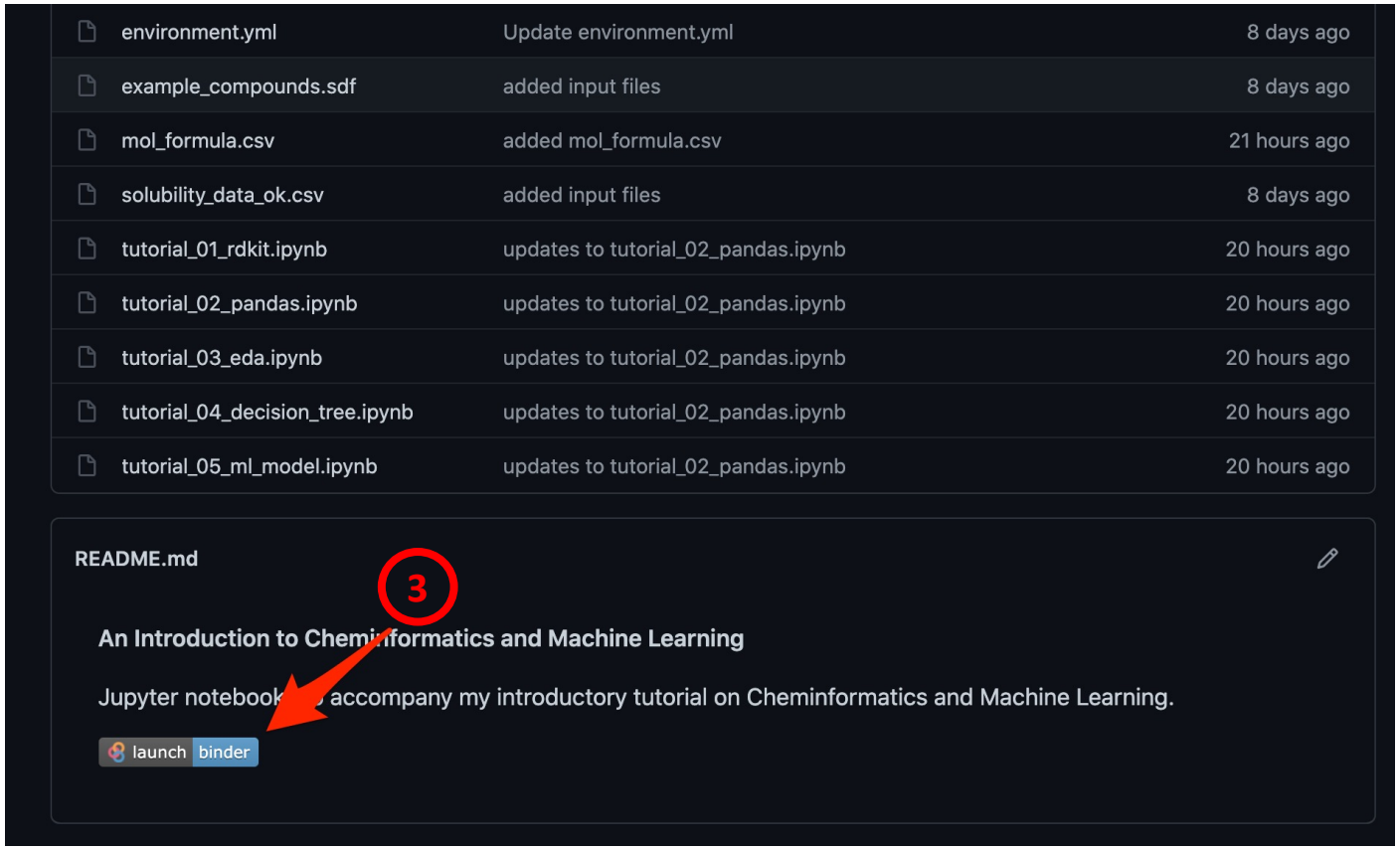
Cheminformatics With Open-Source Software

Pat Walters

August 19, 2021

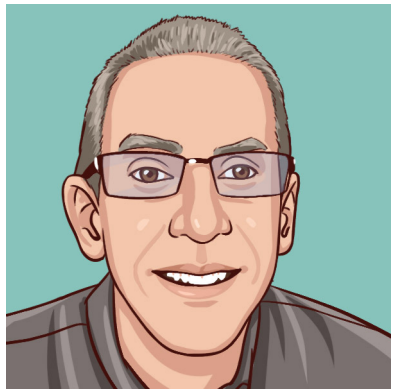
Accessing the Interactive Materials For This Talk

1 https://github.com/PatWalters



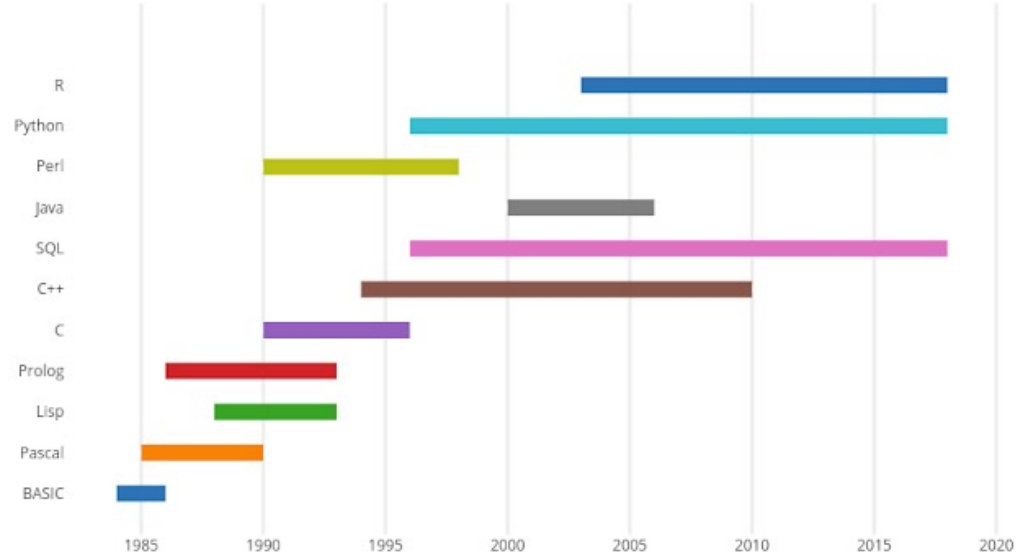
These 3 steps should enable you to launch the Binder environment so that you can run the Jupyter notebooks for this talk

About Me



25 years in drug discovery
35 years writing software
A couple of years of blogging

Cheminformatics
Machine learning



ELSEVIER

Journal of Molecular Graphics

Volume 11, Issue 2, June 1993, Pages 106-111

Papers

MOUSE: A teachable program for learning in conformational analysis

Daniel P. Dolata, W.Patrick Walters

About You

A small amount of experience programming in Python

Knowledge of what organic molecules are

Curiosity and a desire to learn

What We're Going To Cover

Exploratory data analysis

- **A brief introduction to Jupyter notebooks**
- **A quick overview of the RDKit**
- **A lightning tour of the Pandas library for data analysis**

A classification model example

- **Build a decision tree**

A regression model

- **Predict aqueous solubility**

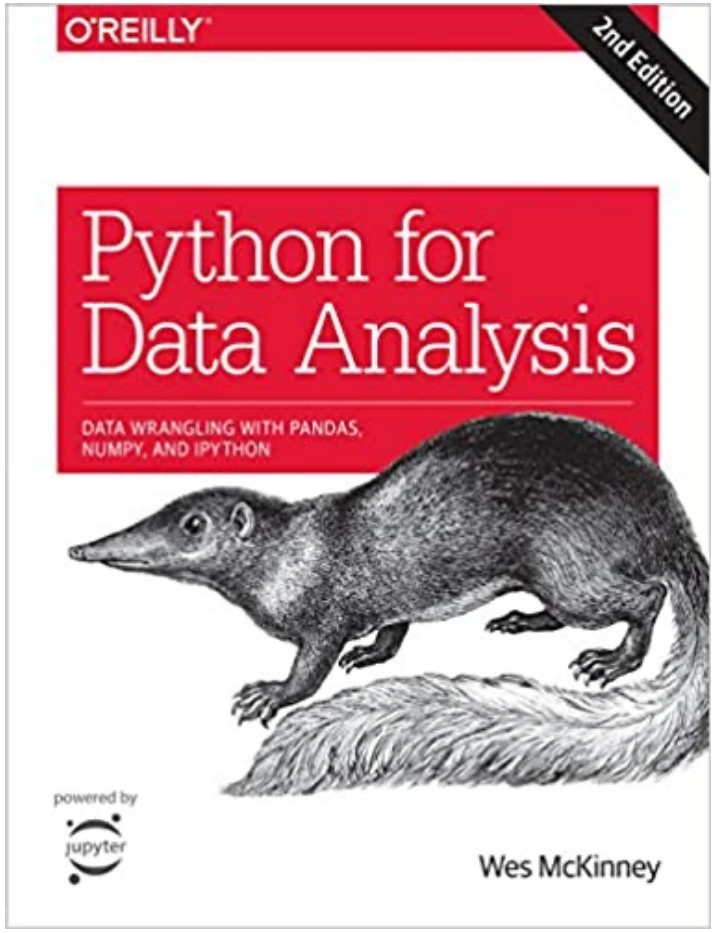
What We’re Not Going To Cover

Neural networks
Learned molecular representations
Generative models

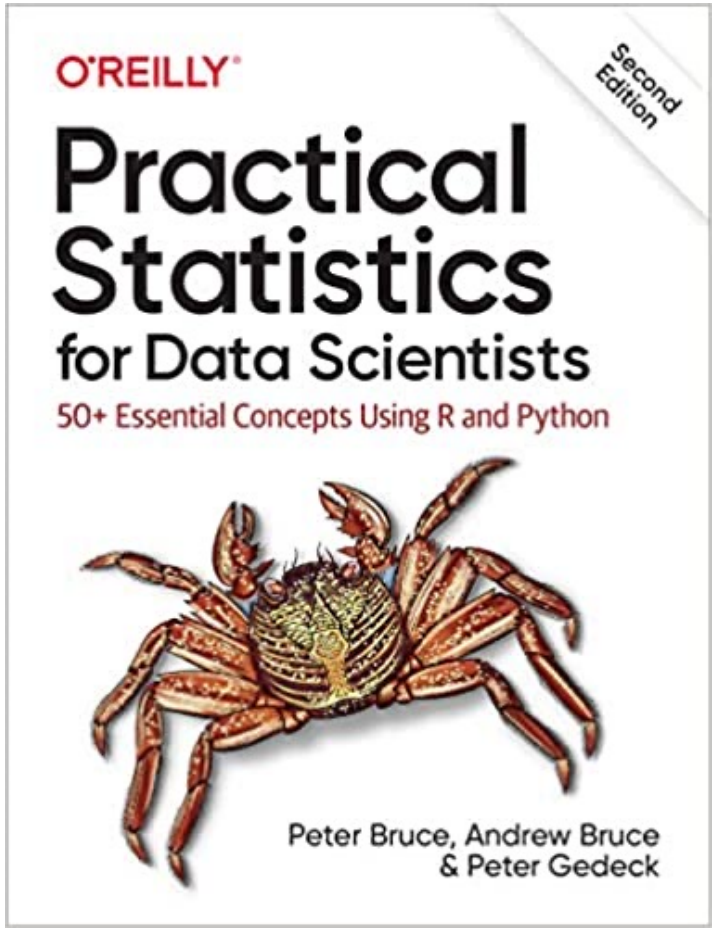
Applicability domain
Model confidence

A lot theory

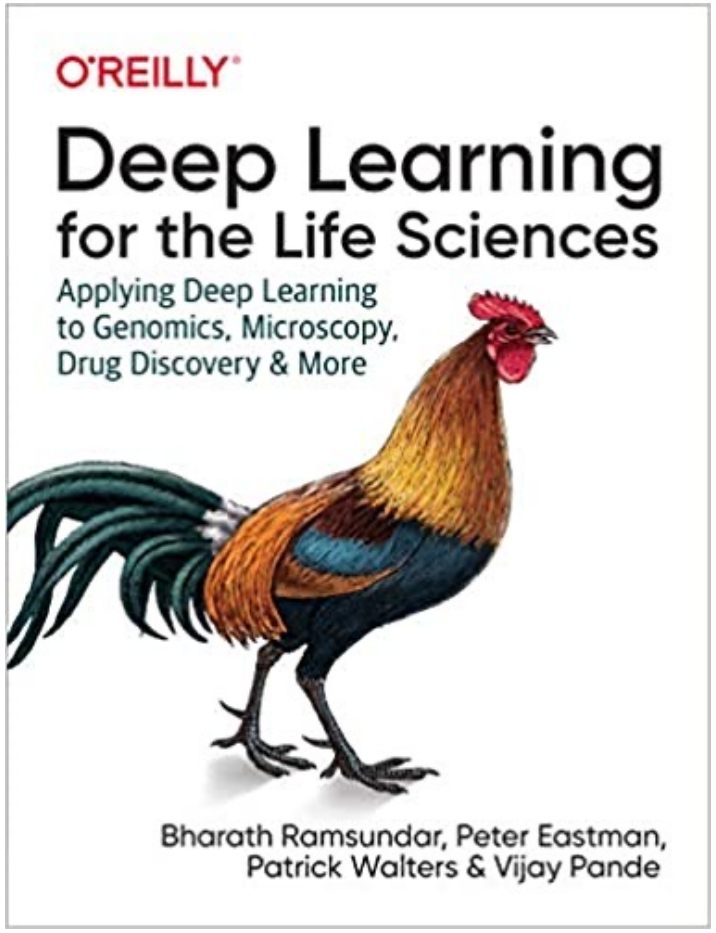
Recommended Reading



https://www.amazon.com/Python-Data-Analysis-Wrangling-IPython/dp/1491957662/



https://www.amazon.com/Practical-Statistics-Data-Scientists-Essential/dp/149207294X/



https://www.amazon.com/Deep-Learning-Life-Sciences-Microscopy/dp/1492039837

The RDKit Cookbook

RDKit Cookbook

Introduction

What is this?

This document provides example recipes of how to carry out particular tasks using the RDKit functionality from Python. The contents have been contributed by the RDKit community, tested with the latest RDKit release, and then compiled into this document. The RDKit Cookbook is written in reStructuredText, which supports Sphinx doctests, allowing for easier validation and maintenance of the RDKit Cookbook code examples, where appropriate.

What gets included?

The examples included come from various online sources such as blogs, shared gists, and the RDKit mailing lists. Generally, only minimal editing is added to the example code/notes for formatting consistency and to incorporate the doctests. We have made a conscious effort to appropriately credit the original source and authors. One of the first priorities of this document is to compile useful **short** examples shared on the RDKit mailing lists, as these can be difficult to discover. It will take some time, but we hope to expand this document into 100s of examples. As the document grows, it may make sense to prioritize examples included in the RDKit Cookbook based on community demand.

Feedback and Contributing

If you have suggestions for how to improve the Cookbook and/or examples you would like included, please contribute directly in the source document (the .rst file). Alternatively, you can also send Cookbook revisions and addition requests to the mailing list: <rdkit-discuss@lists.sourceforge.net> (you will need to subscribe first).

Note

The Index ID# (e.g., **RDKitCB_##**) is simply a way to track Cookbook entries and image file names. New Cookbook additions are sequentially index numbered, regardless of where they are placed within the document. As such, for reference, the next Cookbook entry is **RDKitCB_35**.

Open-Source Cheminformatics and Machine Learning

Table of Contents

https://www.rdkit.org/docs/Cookbook.html

Useful Blogs

Practical Cheminformatics - This is a blog where I post once a month or so. These posts typically contain code that demonstrates various aspects of cheminformatics; clustering, machine learning, data visualization, etc. I occasionally throw in posts containing opinions on things like AI and getting a job.

Is Life Worth Living - A great blog from Iwatobipen (aka pen), whose posts are chock full of great code examples. Pen always seems to be up on the latest methods and posts interesting examples on a variety of topics ranging from quantum chemistry to machine learning.

The RDKit Blog - Greg Landrum is the primary contributor to, and BDFL, of the RDKit. In addition to the latest and greatest features in the RDKit, Greg's posts also touch on a number of key issues in Cheminformatics, such as dealing with unbalanced datasets and the impact of fingerprint folding on similarity searching.

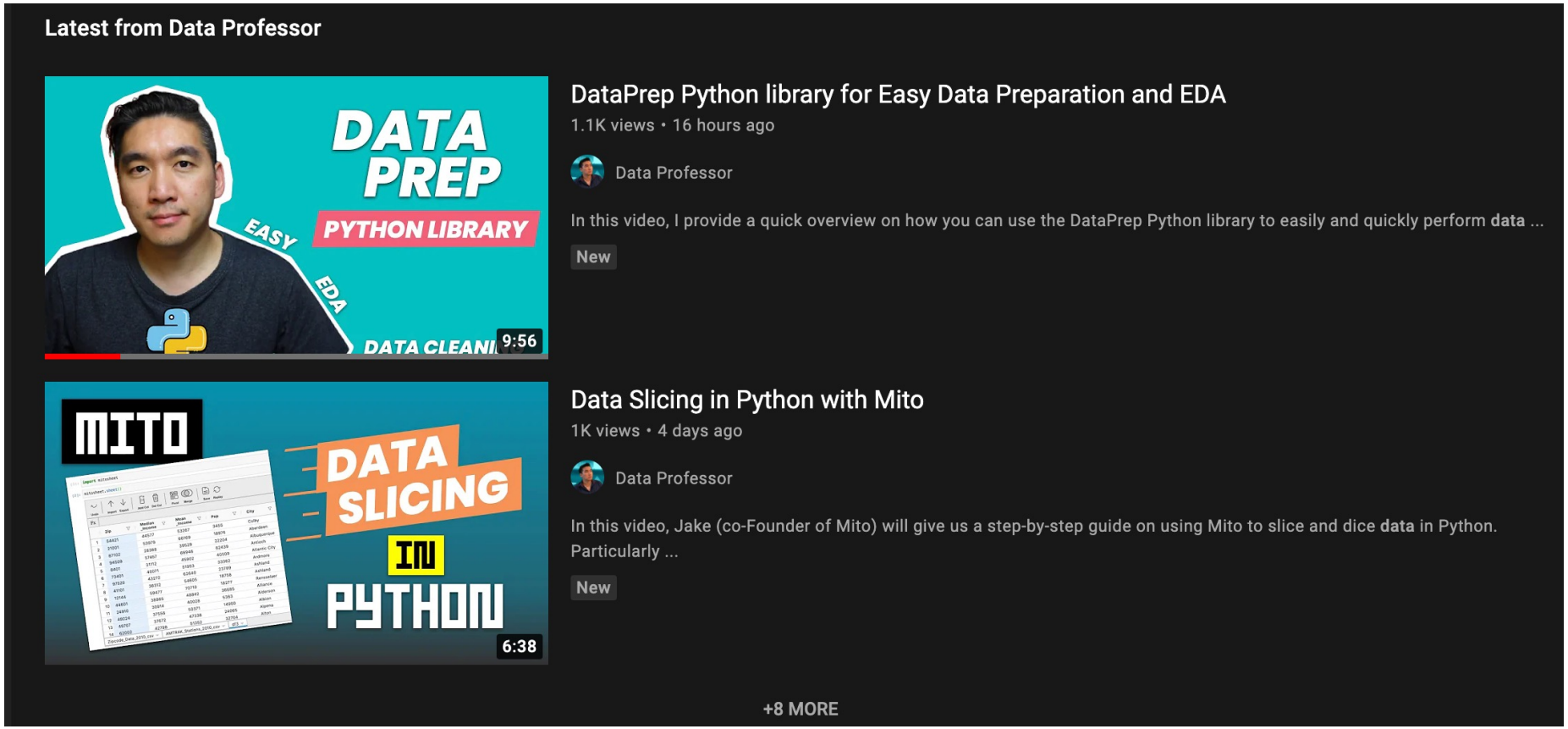
Reverie Labs Engineering Blog - The gang at Reverie Labs is doing some of the best work on applying machine learning in drug discovery. Their blog provides useful insights for those applying machine learning at scale.

The OpenBench Blog - A number of thoughtful posts on ADME modeling and the ways that we validate models.

Cheminformania - A set of very practical posts by Esben Jannik Bjerrum and friends that primarily focus on the applications of deep learning in drug discovery. These posts provide several useful code examples.

YouTube

https://www.youtube.com/results?search_query=data+professor



AI and “The Rise of the Machines”

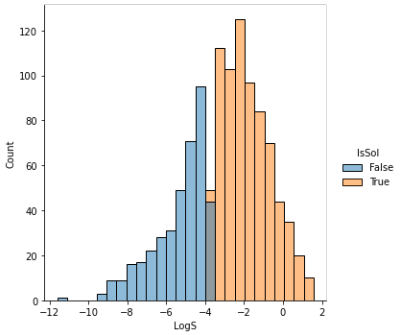
What is Machine Learning?

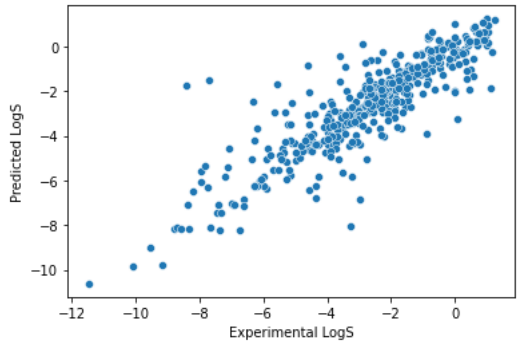
Machine learning is all about labeling things using examples.

Cassie Kozyrkov, Google

Supervised vs Unsupervised Machine Learning

Supervised ML

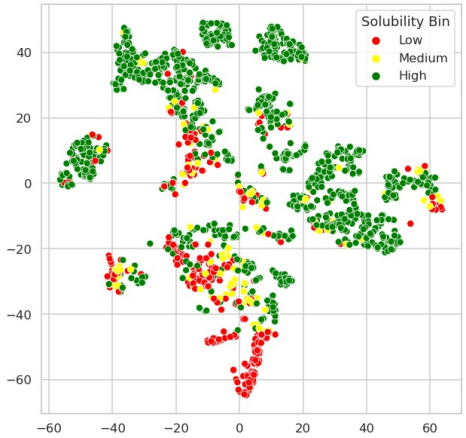


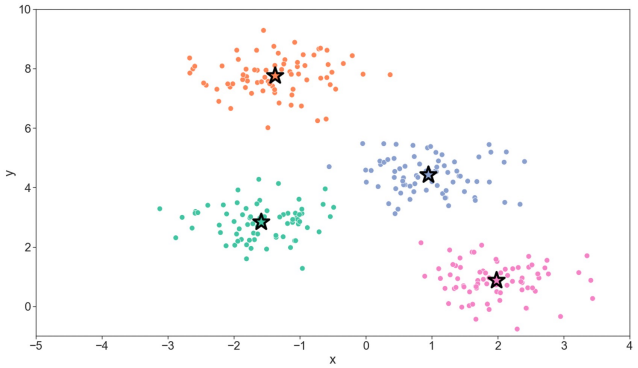


Classification **Regression**

Predict

Unsupervised ML



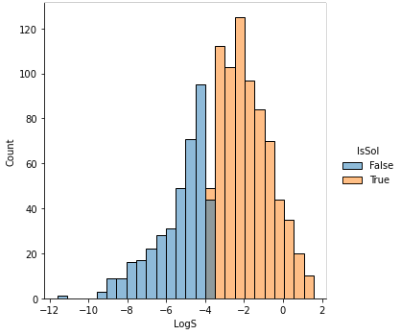


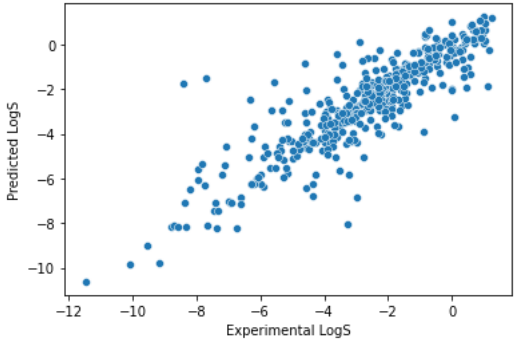
Dimensionality Reduction **Clustering**

Group and Understand

Supervised vs Unsupervised Machine Learning

Supervised ML

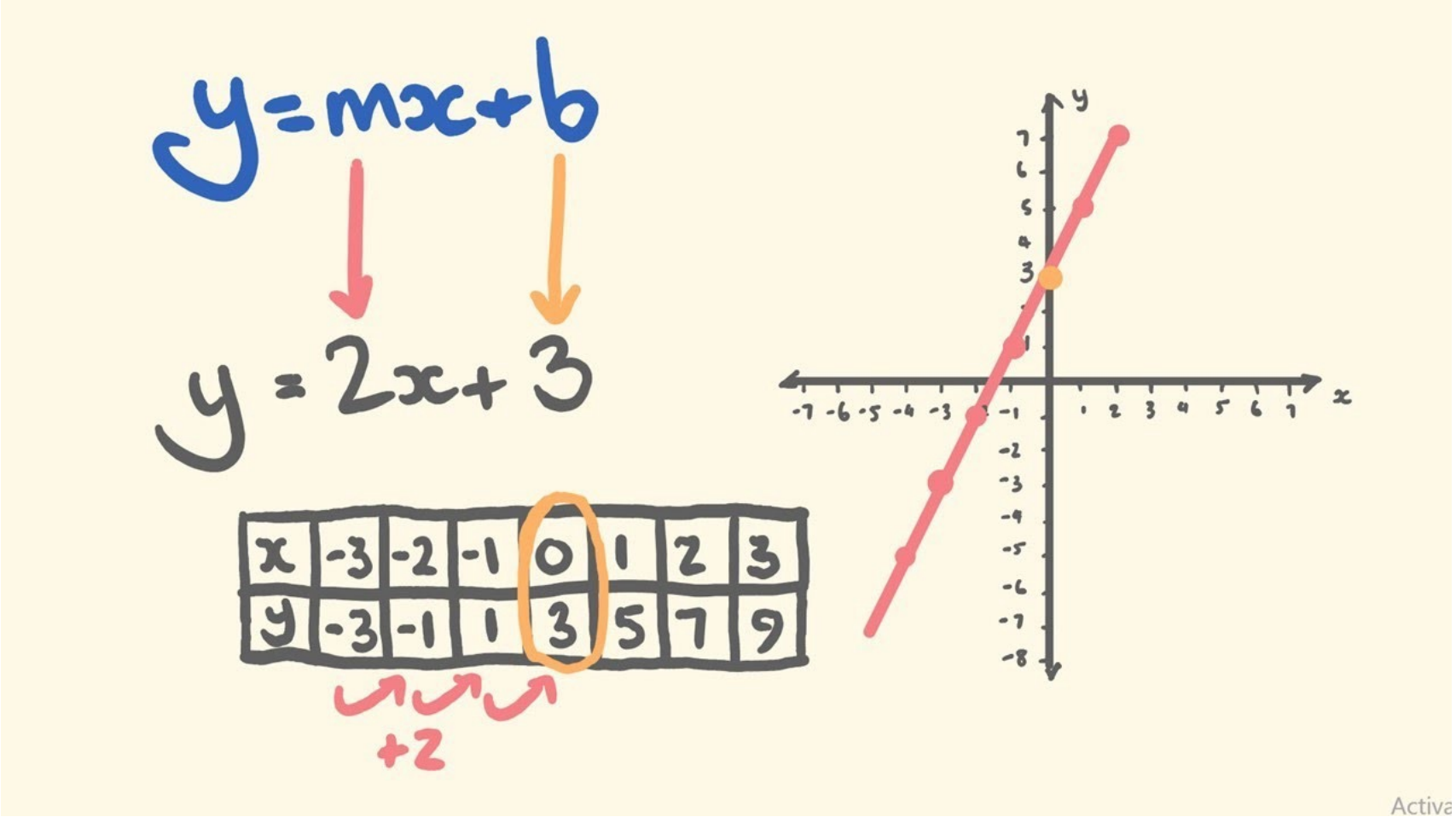




Classification **Regression**

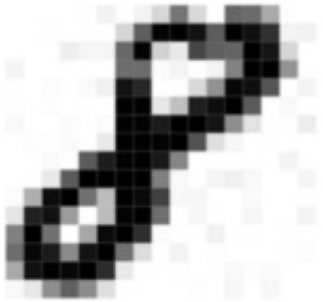
Predict

What Are the Observables (X)? What is Being Predicted (Y)?



Much of Computation is Based on Vector Representations

Images



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```

Text

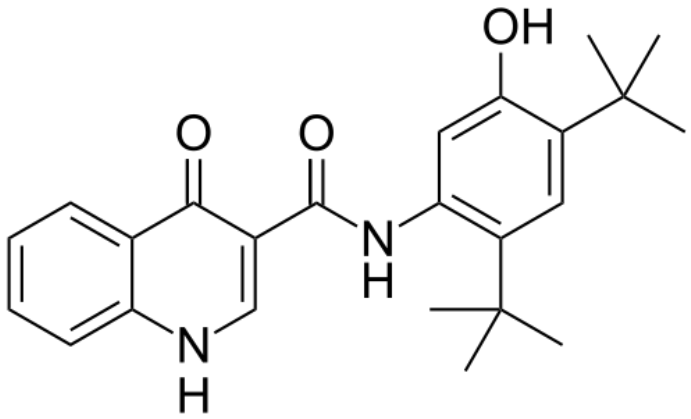
Word	Index
It	1
was	2
the	3
best	4
of	5
times	6
worst	7
age	8
wisdom	9
foolishness	10

	1	2	3	4	5	6	7	8	9	10
	it	was	the	best	of	times	worst	age	wisdom	foolishness
It was the worst of times	1	1	1	0	1	1	1	0	0	0
it was the best of times	1	1	1	0	1	0	0	1	1	0
it was the age of foolishness	1	1	1	0	1	0	0	1	0	1

https://medium.com/@ageitgey/machine-learning-is-fun-part-3-deep-learning-and-convolutional-neural-networks-f40359318721

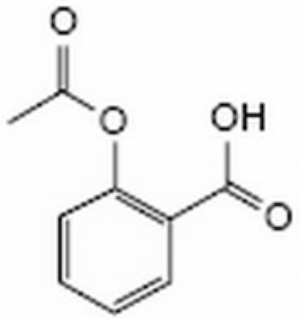
Can We Create a Similar Vector Representation of a Molecule?

Encode molecular features in computer readable format



1	0	0	1	1	1	0	0	1	0	0	1	1	1	0	0

Chemical Fingerprints Represent Molecular Features



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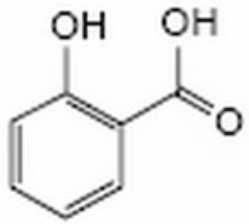
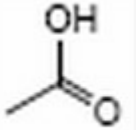
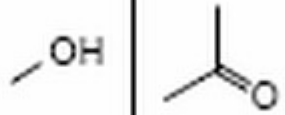
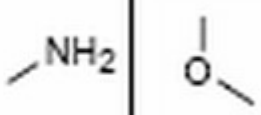
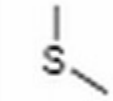
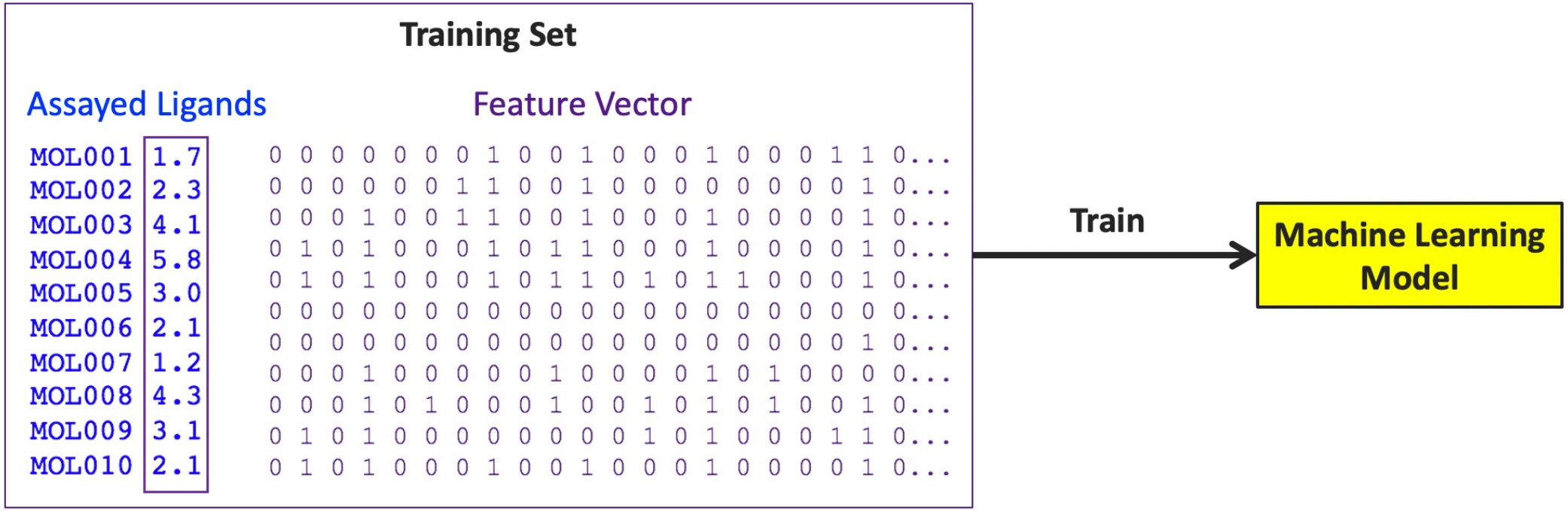


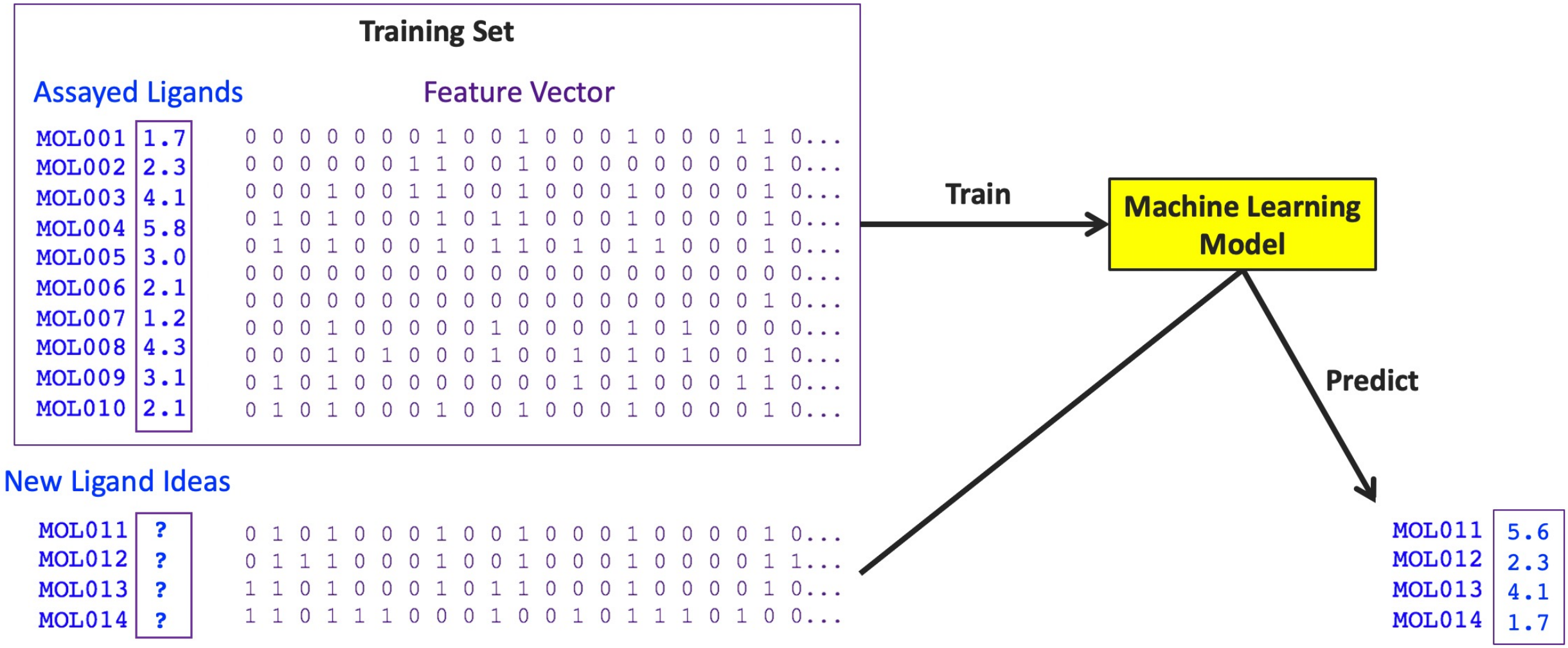
2

1	1	1	0	1	1	0	1	0
2	1	1	0	1	0	0	0	0
								

Training a Machine Learning Model



Making Predictions With a Machine Learning Model



Important Jupyter Notebook Keyboard Shortcuts

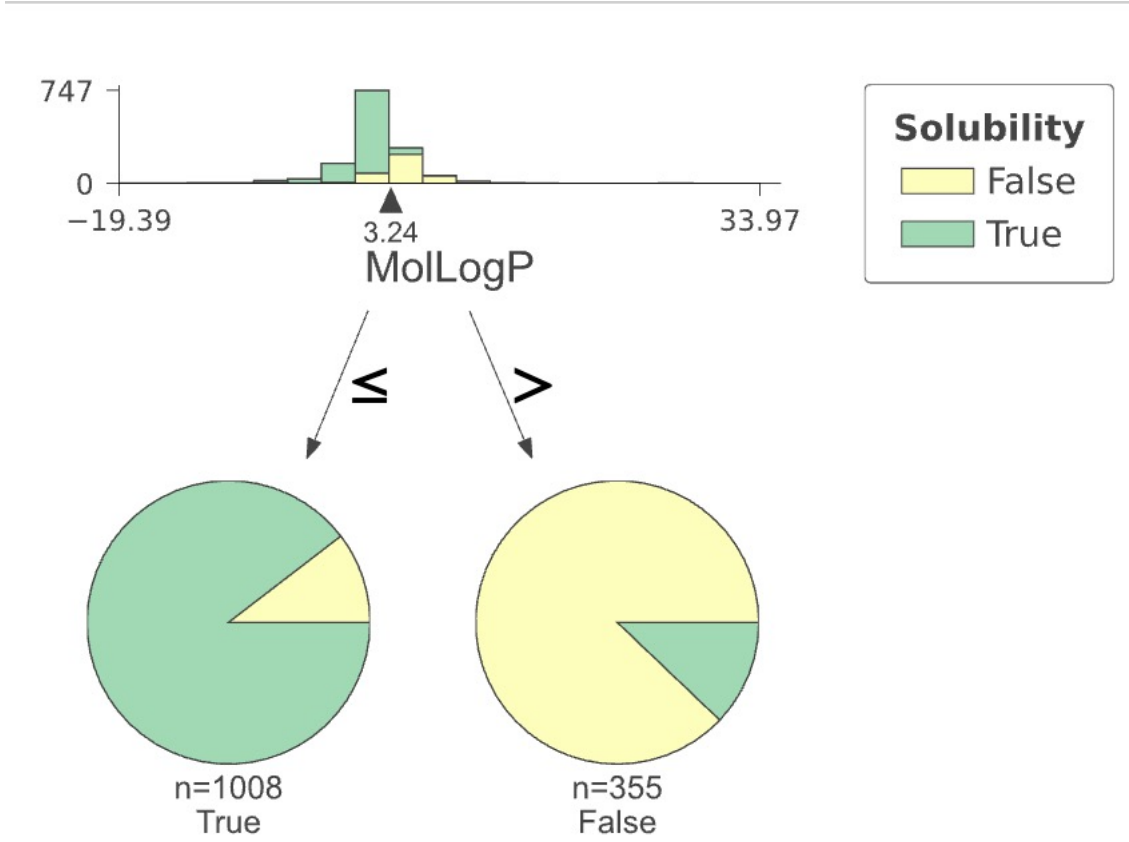
Esc-a	Insert cell above
Esc-b	Insert cell above
Esc-x	Delete cell(s)
Esc-m	Convert cell type to Markdown
Esc-y	Convert cell type to Code

Hands-on Part 1

The Decision Tree – A Simple ML Classifer

Molecular Descriptors

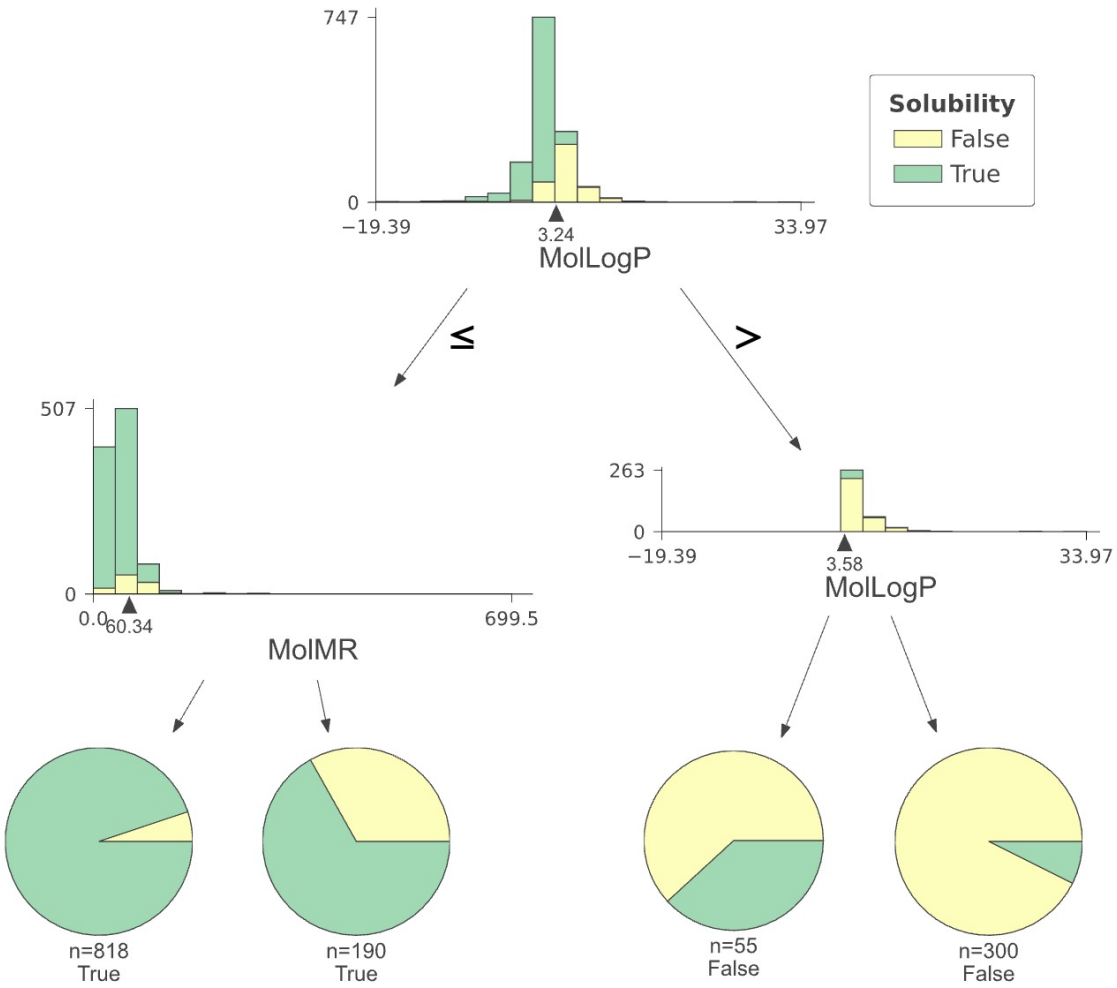
- MolWt
- MolLogP
- MolMR
- HeavyAtomCount
- NumHAcceptors
- NumHDonors
- NumHeteroatoms
- NumRotatableBonds
- NumValenceElectrons
- NumAromaticRings
- NumSaturatedRings
- NumAliphaticRings
- RingCount
- TPSA
- LabuteASA



Increase the Decision Tree Depth to 2

Molecular Descriptors

- MolWt
- MolLogP
- MolMR
- HeavyAtomCount
- NumHAcceptors
- NumHDonors
- NumHeteroatoms
- NumRotatableBonds
- NumValenceElectrons
- NumAromaticRings
- NumSaturatedRings
- NumAliphaticRings
- RingCount
- TPSA
- LabuteASA



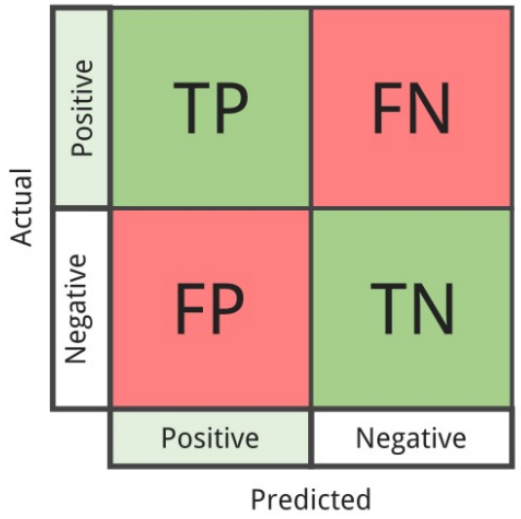
Select Decision Tree Splits Using Gini Impurity

$$G = 1 - \sum_{k=1}^{n} {p_k}^2$$

Gini impurity

0.00 **0.18** **0.24** **0.40** **0.50**

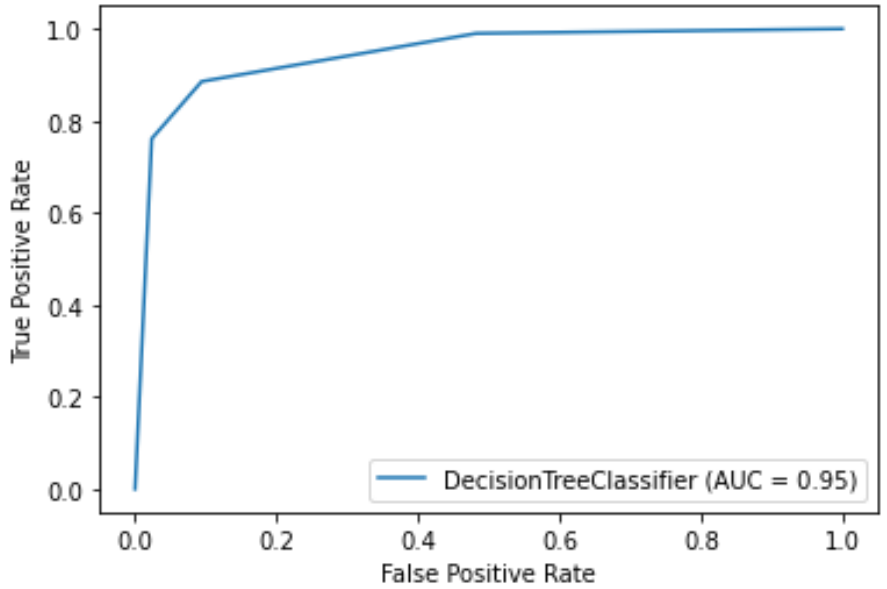
Evaluating Classification Models



Confusion Matrix

$$TPR = \frac{TP}{TP + FN}$$

$$FPR = \frac{FP}{FP + FN}$$



ROC AUC Curve

$$\text{MCC} = \frac{TP \times TN - FP \times FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}$$

Matthews Correlation Coefficient

$$\kappa = \frac{2 \times (TP \times TN - FN \times FP)}{(TP + FP) \times (FP + TN) + (TP + FN) \times (FN + TN)}$$

Cohen's Kappa

Building A Classification Model With SciKit Learn

```
train, test = train_test_split(df)
train_X = train[descriptors]
train_y = train.experiment
test_X = test[descriptors]
test_y = test.experiment

my_model = RandomForestRegressor()
my_model.fit(train_X, train_y)
pred = my_model.predict(test_X)

auc = roc_auc_score(test_y,pred)
mcc = matthews_corrcoef(test_y,pred)
kappa = cohen_kappa_score(test_y,pred)
```

Construct training and test sets

Build a predictive model

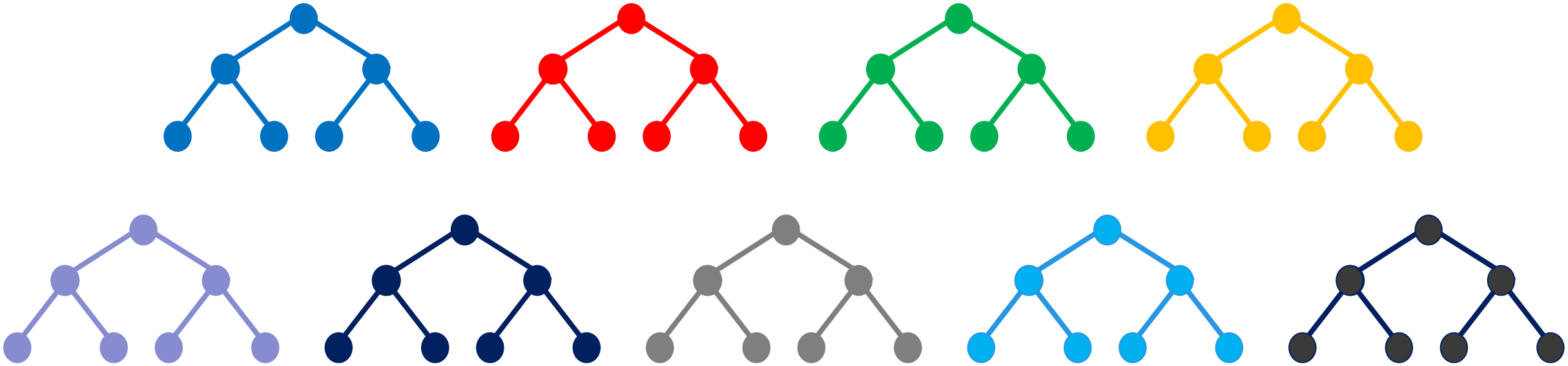
Evaluate the predictive model

Hands-on Part 2

Ensemble models

Random Forest
Extreme Gradient Boosting (XGBoost)
CatBoost
Light Gradient Boosting Machines (LightGBM)

Tend to work well on tabular data



Building A Regression Model With SciKit Learn

```
train, test = train_test_split(df)
train_X = train[descriptors]
train_y = train.experiment
test_X = test[descriptors]
test_y = test.experiment
```

Construct training and test sets

```
my_model = RandomForestRegressor()
my_model.fit(train_X, train_y)
pred = my_model.predict(test_X)
```

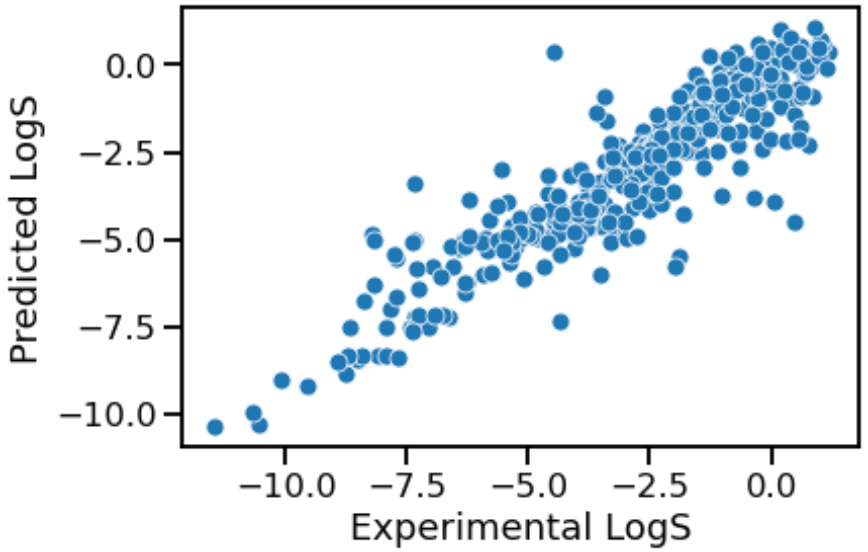
Build a predictive model

```
r2 = r2_score(test_y,pred)
rmse = mean_squared_error(test_y,pred,
squared=False)
```

Evaluate the predictive model

Hands-on Part 3

Evaluating Regression Models



$$\bar{y} = \frac{1}{n}\sum_{i=1}^{n} y_i$$

$$SS_{\text{tot}} = \sum_i (y_i - \bar{y})^2$$

$$SS_{\text{res}} = \sum_i (y_i - f_i)^2 = \sum_i e_i^2$$

$$R^2 = 1 - \frac{SS_{\text{res}}}{SS_{\text{tot}}}$$

Coefficient of Determination

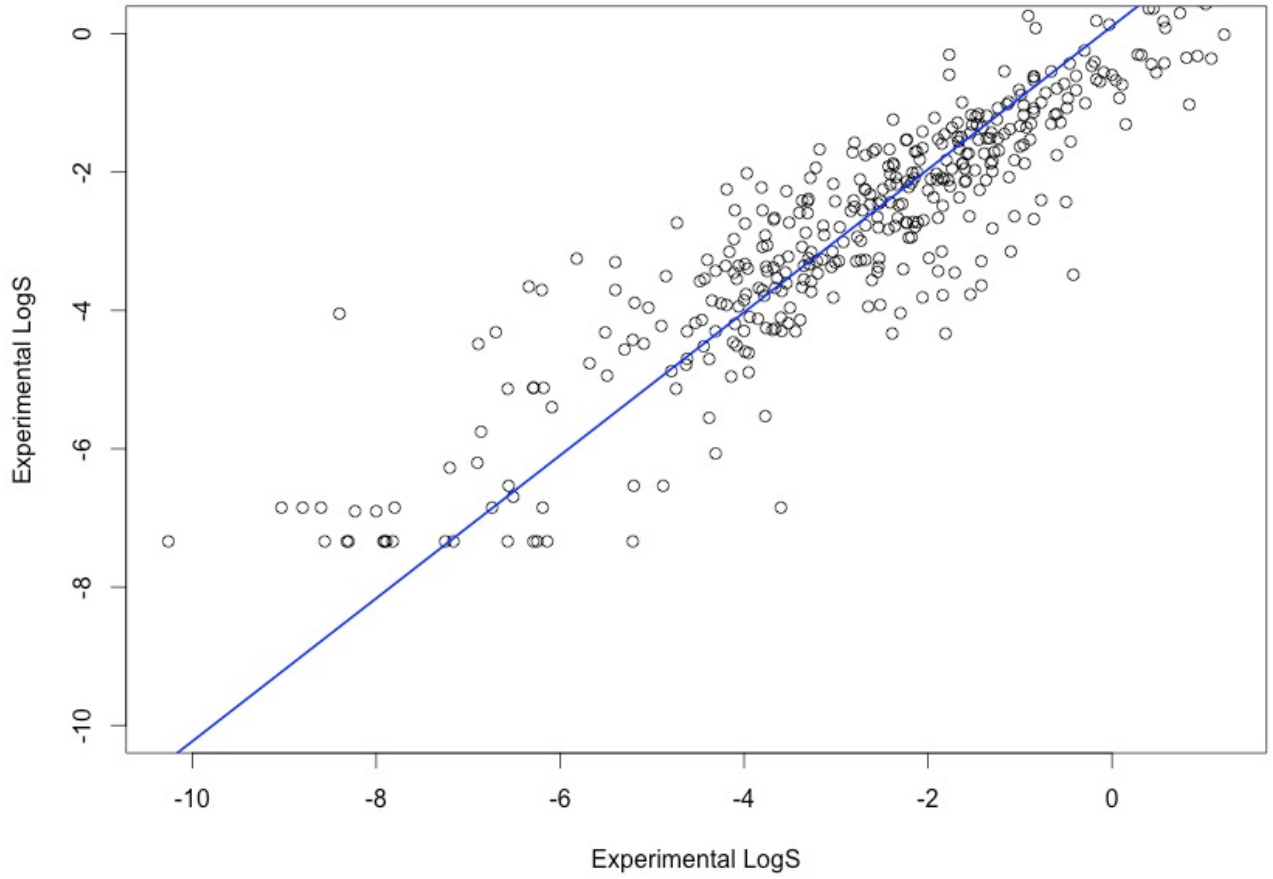
$$\text{RMSD} = \sqrt{\frac{\sum_{t=1}^{T} (\hat{y}_t - y_t)^2}{T}}.$$

Root Mean Squared Deviation (Error)

Evaluating Correlation

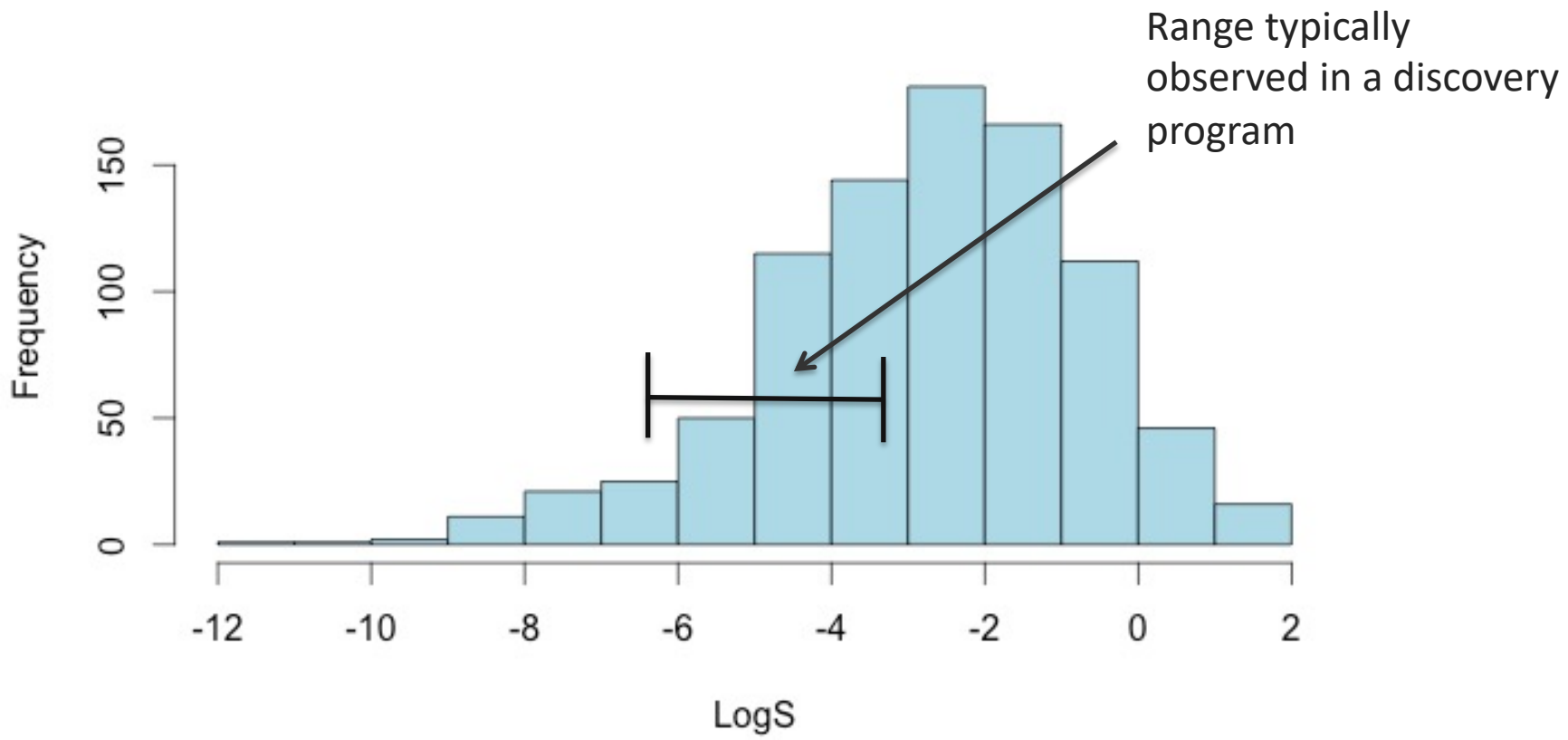
R^2=0.8

Median Absolute Error =0.54



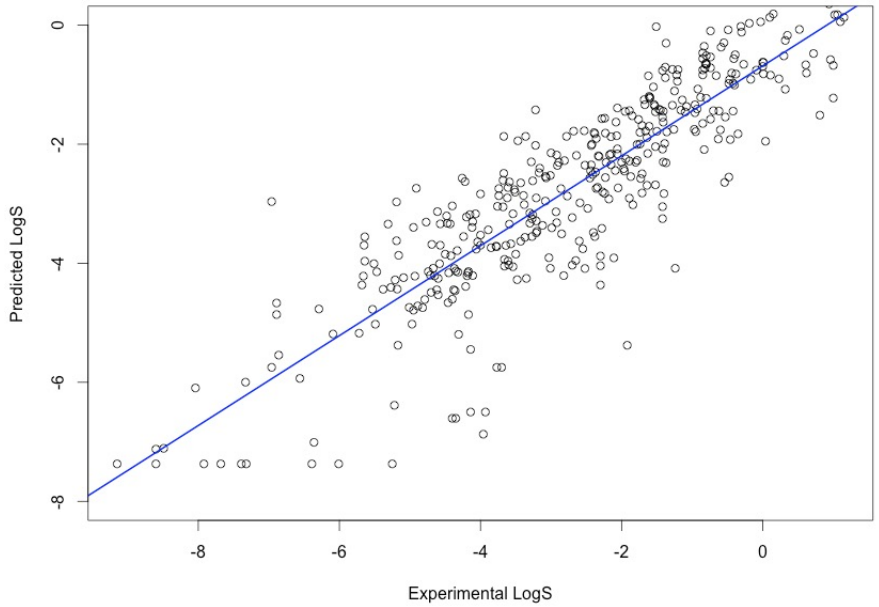
Let's Understand the Data

- This data spans a very wide range
- Much wider than typically observed in a drug discovery program

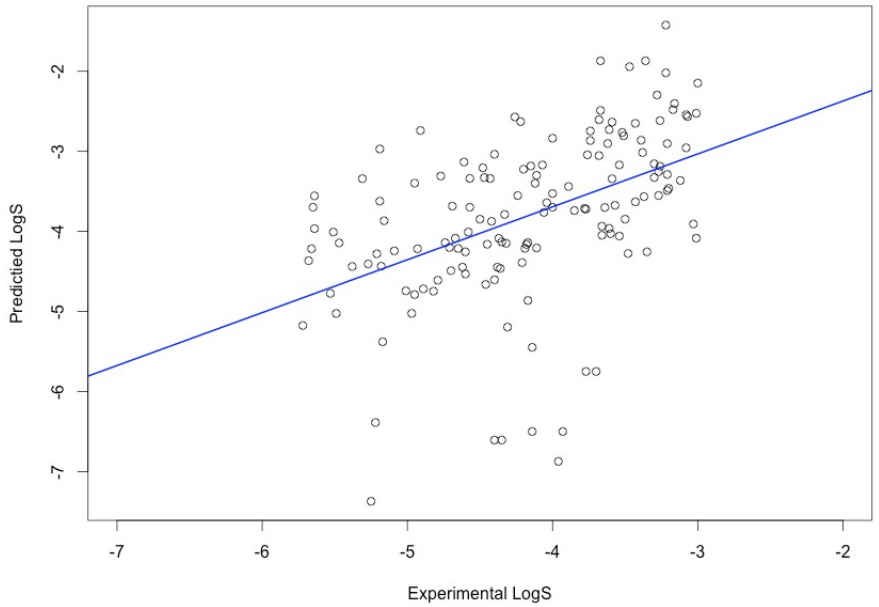


Correlation Changes With Dynamic Range

This is the same dataset. On the left we consider the entire set, which has an unrealistically large (~10 log) dynamic range. On the right we consider a more realistic subset with a 3 log dynamic range. Note the change in correlation.

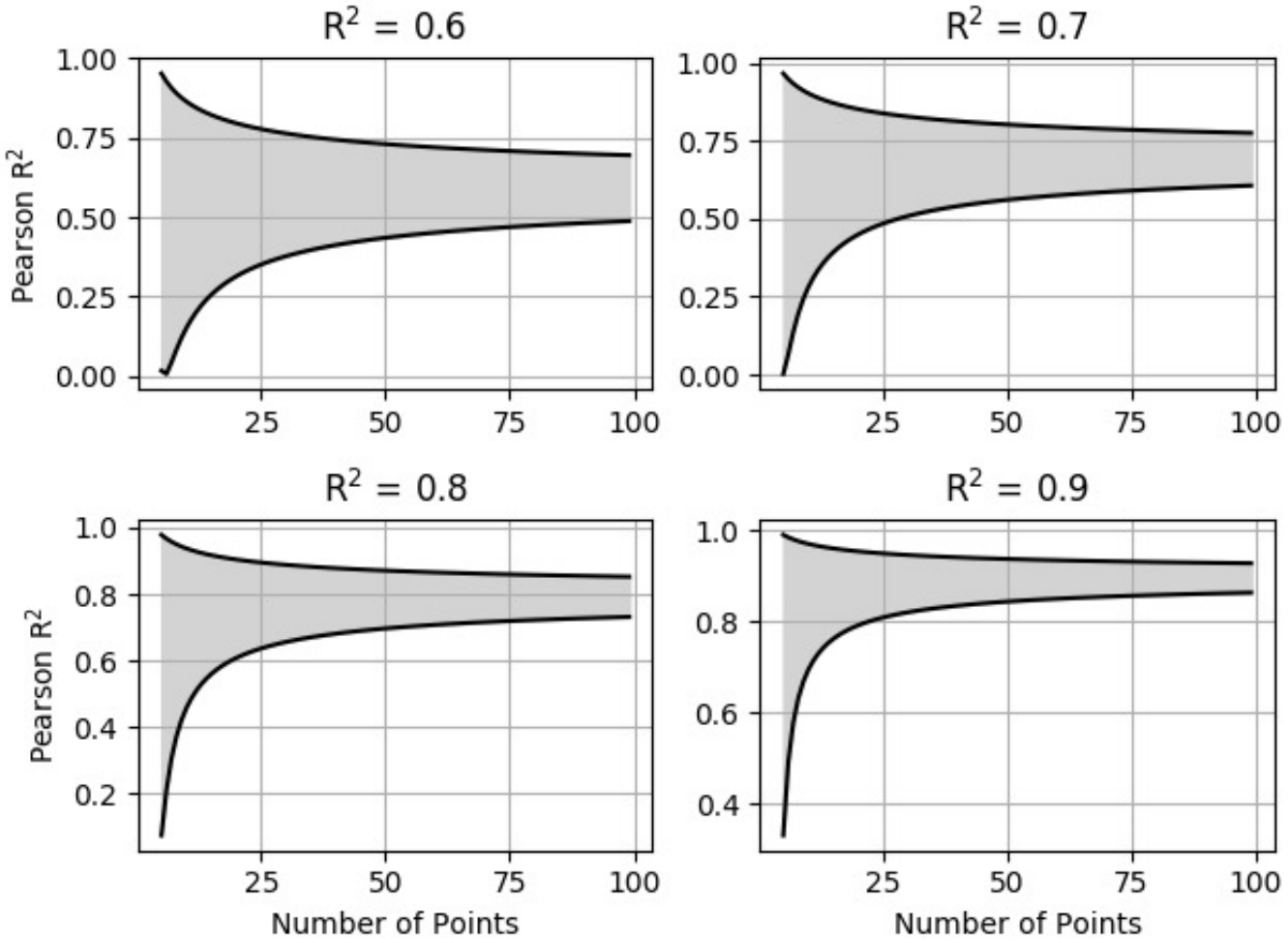


R^2=0.76
MAE=0.55



R^2=0.22
MAE=0.69

Remember That Correlation Have Confidence Limits



https://pingouin-stats.org

Pingouin is an open-source statistical package written in Python 3 and based mostly on Pandas and NumPy. Some of its main features are listed below. For a full list of available functions, please refer to the API documentation.

1. ANOVAs: N-ways, repeated measures, mixed, ancova
2. Pairwise post-hocs tests (parametric and non-parametric) and pairwise correlations
3. Robust, partial, distance and repeated measures correlations
4. Linear/logistic regression and mediation analysis
5. Bayes Factors
6. Multivariate tests
7. Reliability and consistency
8. Effect sizes and power analysis
9. Parametric/bootstrapped confidence intervals around an effect size or a correlation coefficient
10. Circular statistics
11. Chi-squared tests
12. Plotting: Bland-Altman plot, Q-Q plot, paired plot, robust correlation…